Remarks

The Amendments to the Claims

Claim 10 has been amended to recite a "method" in place of a "method of screening compounds to identify potential anti-cancer agents." Claim 10 has also been amended to recite a step of "determining if the test compound preferentially inhibits growth of the first cell line relative to the second cell line" in place of "identifying as a potential anti-cancer agent a test compound which preferentially inhibits growth of the first cell line relative to the second cell line." The specification supports these amendments at page 10, lines 1-2: "The ratio of inhibition or killing [of securin-defective cells compared to securin-proficient cells] can be determined by any means known in the art." These amendments also do not narrow the scope of claim 10.

Claim 10 has amended to recite that the cell lines employed in the method are "two isogenic mammalian cell lines, wherein the first cell line is homozygous securin-defective and the second cell line is securin-proficient" in place of "the two isogenic mammalian cell lines of claim 5." Previously canceled claim 5 supports this amendment.

None of these amendments introduces new matter.

The Rejection of Claims 10-18 and 23 Under 35 U.S.C. § 112, Second Paragraph

Claims 10-18 and 23 have been rejected under 35 U.S.C. § 112 second paragraph as being indefinite. Applicants respectfully traverse.

Claim 10, and thus dependent claims 11-18 and 23, have been rejected as indefinite for reciting dependency upon canceled claim 5. Claim 10 has been amended to recite the elements of canceled claim 5.

Applicants respectfully request withdrawal of this rejection.

The Rejection of Claims 10-18 and 23 Under 35 U.S.C. § 112, First Paragraph

Claims 10-18 and 23 stand rejected under 35 U.S.C. § 112, first paragraph, as not enabled. Applicants respectfully traverse.

Claim 10 is the only independent claim of the rejected claim set. Amended claim 10 is directed to a method which determines whether a test compound preferentially inhibits growth of a homozygous securin-defective cell line relative to a securin-proficient cell line.

The enablement requirement sets forth that the specification must describe how to make and use the claimed invention. 35 U.S.C. § 112, ¶ 1. The claims are enabled so long as the specification teaches one of skill in the art how to make and use the invention without having to resort to undue or unreasonable experimentation. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). The test to determine whether experimentation is undue is not merely quantitative, since a considerable amount of experimentation is permissible if it is merely routine or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *Id.* A patent need not teach, and preferably omits what is well known in the art. *In re Buchner*, 929 F.2d 660 (Fed. Cir. 1991).

The Office Action asserts that the claims are not enabled because the specification does not disclose any test compounds that have been identified as potential anti-cancer agents by the

claimed methods or guide one skilled in the art to particular test compounds that could reasonably be expected to be potential anti-cancer agents by, for example, structural or biochemical characteristics. The Office Action alleges:

> The specification does not teach a particular test agent which would inhibit the growth of the first cell line relative to the second cell line. The specification does not teach any structural or biochemical requirements which should be present in the genus of test compounds which would allow one of skill in the art to select a set of test compounds and subject them to the instant method with a reasonable expectation of success of identifying an agent which would inhibit the growth of the first cell line relative to the second cell line. Further, the specification does not teach a partial structure coupled with a biochemical characteristic which would provide a reasonable expectation of success to one of skill in the art for the selection of test agents which would inhibit the cell lines as claimed. Given the lack of guidance in the specification for how to find a test agent which would function as claimed, one of skill in the art would be subject to undue experimentation in order to carry out the claimed methods.

Page 3, lines 8-19.

To expedite prosecution, the claims have been amended to recite methods comprising the steps of contacting a test compound with a first cell line, which is homozygous securin-defective, and a second cell line, which is securin-proficient, and determining if the test compound preferentially inhibits growth of the first cell line relative to the second cell line. Claim 10, as amended and as originally filed, is not directed to compounds with anti-cancer activity nor to compounds likely to have anti-cancer activity. Therefore, the specification need not disclose such compounds to enable the claimed methods. Any compound can be tested in the claimed method without regard to any *a priori* knowledge about it. The specification teaches that virtually any compound can be used as a test compound to contact the two isogenic cell lines:

> Potential therapeutic agents which can be tested include agents which are known in the art to have a pharmacological activity or can be compounds whose pharmacological activity is unknown. Compounds which can be tested include substances which are naturally occurring or which are designed in the laboratory, including members of small molecule libraries, protein libraries, nucleic acid libraries, etc. Test substances can be isolated from microorganisms, animals, or plants, or be produced recombinantly or by chemical synthesis.

Page 9, lines 5-12. The specification also teaches that known anti-tumor agents can be used in the methods:

> Therapeutic agents with known anti-tumor effects, such as cytosine arbinoside, fluorouracil, methotrexate or aminopterin, an anthracycline, mitomycin C, vinca alkaloids, demecolcine, etoposide, mithramycin, or an antitumor alkylating agent such as chlorambucil or malphalan can be tested for their efficacy against homozygous securin-defective cells.

Page 9, lines 12-16. Thus, any compound can be tested without limitation. No reasons have been put forward by the Patent Office why any compound could not be contacted with the recited isogenic cell lines.

To practice the invention of amended claim 10 one of skill in the art would only need to practice the methods without resorting to undue experimentation. The claimed method comprises a first step of "contacting a test compound with each of two isogenic mammalian cell lines wherein the first cell line is homozygous securin-defective and the second cell line is securin-proficient." To contact such cell lines one of skill in the art must first have access to or be able to produce the cell lines. The specification discloses one such pair of isogenic mammalian cell lines: a HCT116 securin-defective and a HCT116 securin-proficient pair of isogenic mammalian cell lines. Page 15, lines 3-4. The specification also discloses how to prepare other pairs of isogenic mammalian cell lines. The specification cites the methods

disclosed in Waldman et al., 1996; Bunz et al., 1998; Chan et al., 1999; and Rhee et al., 2000. Page 10, lines 12-13. Thus, the specification guides one of skill in the art to well-known methods of producing cells which are homozygous defectives. The specification also provides a working example which describes the method used by the inventors to produce a securin-defective cell line. See Example 5 entitled "Inactivation of the *hSecurin* Locus by Homologous Recombination" at page 23, line 3 to page 24, line 14. Thus the specification guides one of skill in the art to well-known methods and provides an example of producing isogenic securin-defective and securin-proficient mammalian cell lines. In light of the teachings in the specification, it therefore would have merely been routine for one of skill in the art to produce two isogenic mammalian cell lines as recited and would not have required undue experimentation. Notably the Patent Office does not challenge the enablement of the isogenic cell lines.

One of skill in the art would also have been able to contact the two isogenic mammalian cell lines with a test compound as recited in claim 10. It well was known in art that cells can be contacted with a test agent by, *e.g.*, using impregnated paper disks or adding the test agent to the media of cells in culture. As discussed above, the specification discloses that any compound can be used as a test compound. Notably, the Patent Office does not challenge the enablement of contacting cell lines.

Thus, it would have been routine to perform the step of "contacting a test compound with each of two isogenic mammalian cell lines wherein the first cell line is homozygous securin-defective and the second cell line is securin-proficient" as recited in claim 10. The Patent Office has not asserted that any of the recited elements of this step would require undue

experimentation. Because the experimentation would be merely routine, one of skill in the art would not have to resort to undue experimentation to practice the first step of the claim.

The second step of the claimed method recites "determining if the test compound preferentially inhibits growth of the first cell line relative to the second cell line." The specification discloses that any method known in the art may be used to determine whether the test compound inhibits growth of the first cell line relative to the second cell line and provides examples of several assays known in the art. The specification discloses:

> The ratio of inhibition or killing can be determined by any means known in the art. It is well known in the art that viable cells exclude dye. Viable cells can be observed to have an intact membrane and do not stain, whereas dying or dead cells have 'leaky' membranes and do stain. Any dyes known in the art can be used, such as, for example, trypan blue, eosin Y, naphthalene black, nigrosin, erythrosine B, and fast green. The ratio of killed or growth-inhibited homozygous securin-defective cells:securin-proficient cells can also be determined by incorporation of labeled metabolites, such as, for example, ^{3}H-thymidine. Cells can be cultured in medium containing radiolabeled metabolites; uptake or incorporation of the metabolites indicates cells growth.

Page 10, lines 1-10. Notably, the Patent Office does not challenge the enablement of determining cell growth inhibition or assert that it would require undue experimentation to determine if a compound preferentially inhibits growth of a first relative to second cell line.

As discussed above, each of the steps of amended claim 10 could have been practiced without recourse to undue experimentation. The Patent Office challenges whether the specification adequately teaches how to select a test compound that will be identified as having activity in the methods with a reasonable expectation of success. The Patent Office faults the lack of structural teachings for compounds. However, the method is a function-based identification, and does not rely on any structural parameters. The method can be practiced

without recourse to undue experimentation. One of skill in the art can practice the method with compounds or mixtures of compounds. One of skill can practice the method with compounds whose structures are known or unknown. One can practice the method with any compound at all. Thus the Patent Office's concern is misplaced. Clearly one of ordinary skill in the art can practice the method without recourse to undue experimentation.

Applicants respectfully request withdrawal of the rejection as the Patent Office failed to make a *prima facie* case of non-enablement.

The Rejection of Claims 10-18 and 23 Under 35 U.S.C. § 112, First Paragraph

Claims 10-18 and 23 are rejected under 35 U.S.C. § 112 first paragraph as not adequately described by the specification. Applicants respectfully traverse.

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that the 'inventor invented the claimed invention.'" *The Regents of the University of California v. Eli Lilly and Company*, 19 F.3d 1559, 1566 (Fed. Cir. 1997), emphasis added, citing *Lockwood v. American Airlines, Inc.* 107 F.3d 1565, 1572 (Fed. Cir. 1997); and *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989).

Claim 10 is the only independent claim of the rejected claim set. As discussed above, amended claim 10 is directed to a method which determines if a test compound preferentially inhibits growth of a homozygous securin-defective cell line relative to a securin-proficient cell line. The specification describes the method of claim 10 in sufficient detail such that one skilled in the art would conclude that applicants invented the method of claim 10.

The Office Action asserts, however, that the claims are not described because

> [t]he instant method claims are reliant upon a genus of test compounds. The genus is highly variant because it encompasses a molecule of any structure. The specification does not [provide] any written description of a single test agent which would function in the claimed method.

Page 3, lines 25-27. The claimed invention is not, however, drawn to compounds *per se*. The claimed invention is also not drawn to a method of using compounds. The claimed invention is drawn to methods of determining whether a compound preferentially inhibits growth of a homozygous securin-defective cell line relative to a securin-proficient cell line. The specification, therefore, need not to describe specific compounds that preferentially inhibit growth of a homozygous securin-defective cell line relative to a securin-proficient cell line. The specification need only describe the compounds that are tested in the method. The specification indeed provides a written description of test agents that can be tested in the claimed methods, *i.e.*, as compounds contacted with each of two isogenic mammalian cell lines. See page 9, lines 5-16, quoted above.

The Office Action also asserts that the rejected claims are similar to the claims of U.S. Patent Number 6,048,850, which were invalidated for lack of written description in *University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916 (Fed. Cir. 2004). Therefore, the Office Action concludes that the pending claims, like the claims of the '850 patent, are not adequately described. Office Action at page 5, lines 11-23. Each of the independent claims in the '850 patent were directed to "A method for selectively inhibiting PGHS-2 activity in a human host" by "administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product to [or in] a human host in need of such treatment." *University of Rochester v. G.D.*

Searle & Co., 358 F.3d at 918. The court found that the '850 patent did not describe any non-steroidal compounds that selectively inhibited activity of the PGHS-2. As these compounds were necessary for one of skill in the art to practice the claimed method, *i.e.*, of inhibiting PGHS-2 activity in a human host, the Federal Circuit held the claims invalid for lack of adequate written description. *University of Rochester v. G.D. Searle & Co.*, 358 F.3d at 929.

The claims of the instant application, however, are clearly distinguishable from the claims in the '850 patent. The claims of the instant application are not directed to methods of treatment which require administration of a compound that preferably inhibits growth of a securin-defective cell line relative to a securin-proficient cell line. The claims are directed to methods for identification of such compounds. A molecule that inhibits growth of a securin-defective cell line relative to a securin-proficient cell line is not necessary to practice the claimed methods. In fact, the Federal Circuit addressed the written description of such assay claims in the *University of Rochester* opinion. The court stated: "The only claims that appear to be supported by the specification are claims to assay methods, but those claims were already issued in the '479 patent." *University of Rochester v. G.D. Searle & Co.*, 358 F.3d at 928. The assay claims in the '479 patent are directed to methods for identifying a compound that inhibits prostaglandin synthesis catalyzed by mammalian prostaglandin H synthase-2 (PGHS-2). See U.S. Patent No. 5,837,479 (Exhibit A). The *Rochester* decision demonstrates that an assay claim can be adequately described based on disclosure comparable to that of the present application.

Applicants respectfully request withdrawal of this rejection.

Respectfully submitted,

BANNER & WITCOFF, LTD.

Date: March 11, 2005

By: _____

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-continued

(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(i i) MOLECULE TYPE: peptide

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Arg Xaa Xaa Xaa His
1 5

What is claimed is:

1. A method for identifying a compound that inhibits prostaglandin synthesis catalyzed by mammalian prostaglandin H synthase-2 (PGHS-2) comprising:

(a) contacting a genetically engineered host cell that contains a sequence encoding mammalian PGHS-2 operatively associated with a regulatory sequence that controls gene expression, so that a PGHS-2 gene product is stably expressed by the host cell, with the compound in the presence of a pre-determined amount of arachidonic acid;

(b) measuring the conversion of the arachidonic acid to its prostaglandin metabolite; and

(c) comparing the amount of arachidonic acid converted by the cells exposed to the test compound to the amount of arachidonic acid converted by control cells that were not exposed to the test compound.

2. The method of claim 1 in which the genetically engineered cell contains a sequence encoding mammalian PGHS-2 operatively associated with a regulatory sequence that controls gene expression, so that the mammalian PGHS-2 gene product is stably expressed by the host cell, wherein said sequence does not express PGHS-1.

3. The method of claim 1 in which the genetically engineered cell contains a sequence encoding a mammalian PGHS-2 operatively associated with a regulatory sequence that controls gene expression, so that a PGHS-2 gene product is stably expressed by the host cell, and in which the host cell is a mammalian cell that does not express autologous PGHS-2.

4. The method of claim 1 in which the genetically engineered host cell is designated hPGHS-2 A2.7 p6 Nov. 7, 1993 as deposited with the ATCC having accession no. CRL11923, or progeny thereof expressing PGHS-2.

5. A method for identifying a compound that inhibits prostaglandin synthesis catalyzed by mammalian PGHS-2, but does not inhibit the activity of PGHS-1, comprising:

(a) contacting a genetically engineered cell that expresses mammalian PGHS-2, and not mammalian PGHS-1, with the compound in the presence of a pre-determined amount of arachidonic acid;

(b) contacting a genetically engineered cell that expresses mammalian PGHS-1, and not mammalian PGHS-2, with the compound in the presence of a predetermined amount of arachidonic acid;

(c) measuring the conversion of arachidonic acid to its prostaglandin metabolite; and

(d) comparing the amount of arachidonic acid converted by each cell exposed to the test compound to the amount of arachidonic acid converted by control cells that were not exposed to the test compound, so that compounds that inhibit PGHS-2 and not PGHS-1 activity are identified.

6. The method of claim 5 in which the PGHS-2 expressing cell line is designated hPGHS-2 A2.7 p6 Nov. 7, 1993 as deposited with the ATCC having accession no. CRL11923, or progeny thereof expressing PGHS-2.

7. The method of claim 5 in which the PGHS-1 expressing cell line is designated A1.2 p5 Feb. 20, 1995 as deposited with the ATCC having accession no. CRL11924, or progeny thereof expressing PGHS-1.

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